Tetrahedron Letters 50 (2009) 2964–2966

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An improved method of amide synthesis using acyl chlorides

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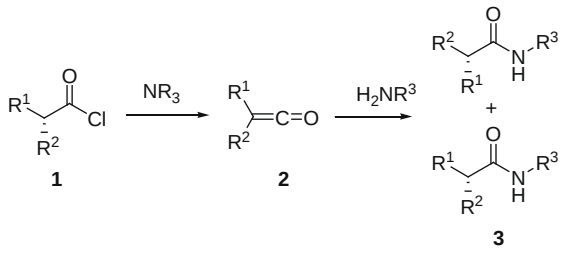
ARTICLE INFO

Article history:
Received 9 March 2009
Revised 30 March 2009
Accepted 31 March 2009
Available online 5 April 2009

ABSTRACT

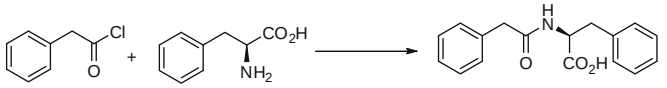
A simple, mild and highly efficient condition for amide synthesis from acyl chlorides has been developed to minimize hydrolysis, racemization and other side reactions. This method should expand capabilities in the peptide coupling area.

The amide functionality exists in numerous biological,[1] pharmaceutical,[2] and agrochemical[3] molecules and has prompted in-depth studies in the formation of the amide bond.[4] Among those methods, the use of acyl chlorides is one of the easiest and most economical. Nevertheless, the value of acyl chlorides in amide coupling is limited due to racemization, hydrolysis, deprotection, and other side reactions. We were inspired by the need for a cost-effective yet robust amide coupling method for complex molecules in our recent research projects. The literature methods using acyl chlorides have significant limitations. When aqueous inorganic bases are used, water induces hydrolysis which can be overwhelming if the amine is not very reactive. When organic bases are employed, ketene formation is often observed if an α-proton is present. This ketene intermediate will necessarily lead to the loss of chirality (Scheme 1) and other side reactions.[4] If anhydrous, non-basic conditions for amide bond formation could be found, these limitations in the use of acyl chlorides might be overcome. Herein, we report a simple, scalable, and highly efficient method of amide formation using weak inorganic base as acid scavenger under anhydrous condition with significant improvement over known procedures.



Scheme 1. Mechanism for chirality loss.

Table 1
Background reactions and coupling results of different bases[a]



Entry	Base (equiv)	Solvent	Yield (%)
1	2.0 TEA	THF	20
2	2.0 aq NaOH	THF	84
3	2.0 K_3PO_4	THF	81
4	2.5 K_3PO_4	THF	87
5	5.0 K_3PO_4	THF	85
6	2.5 Na_2HPO_4	THF	83
7	2.5 K_2SO_3	THF	87
8	2.5 K_2CO_3	THF	73
9	2.5 Cs_2CO_3	THF	79
10	2.5 KOAc	THF	46

[a] Yields were determined by HPLC analysis versus a standard synthesized following literature procedure[7] and the products are purified by flash column chromatography.

We began our investigation with the coupling of phenylacetyl chloride **4** and L-phenylalanine **5** (Table 1). Different inorganic bases were utilized, and the results were compared with those under two literature conditions.[5,6] The coupling led to multiple products and low isolated yields when triethylamine was used as base (entry 1). After switching to aqueous NaOH, 84% of **6** was produced with 16% of phenylacetic acid as the only byproduct of the reaction (entry 2). Commercial K_3PO_4 containing 0.3% water was chosen as the first inorganic base for screening. The reaction with K_3PO_4 was comparatively slower, as **4** was not fully consumed until the mixture had been stirred for 12 h. Using 2.0 equiv of K_3PO_4 afforded 81% yield of **6** and 19% of hydrolyzed byproduct (entry 3). Optimization of stoichiometry showed that 2.5 equiv of base was preferred (entry 4). We were concerned that using additional K_3PO_4 could cause agitation problems due to excessive viscosity

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doi:10.1016/j.tetlet.2009.03.220

Table 2
Coupling results with different solvents[a]

Entry	Base (equiv)	Solvent	Yield (%)
1	2.5 K_3PO_4	THF	87
2	2.5 K_3PO_4	MeCN	57
3	2.5 K_3PO_4	DMF	30
4	2.5 K_3PO_4	Dioxane	75
5	2.5 K_3PO_4	Toluene	46

[a] Yields were determined by HPLC analysis versus a standard synthesized following literature procedure and the products are purified by flash column chromatography.

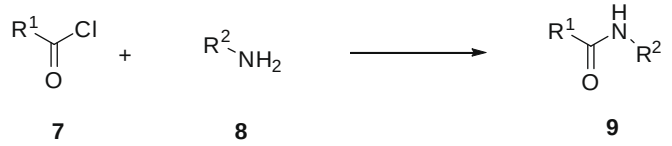
(entry 5). Comparable results were obtained when Na_2HPO_4 and K_2SO_3 were used as bases (entries 6 and 7), while more hydrolysis occurred when K_2CO_3 and Cs_2CO_3 were employed (entries 8 and 9), probably due to the water formed between carbonate and HCl. Higher yields were obtained with Cs_2CO_3 instead of K_2CO_3, which can be contributed to the better solubility of Cs_2CO_3 in THF. Increased hydrolysis occurred when KOAc was used (entry 10). Based on these data, we can conclude that using an inorganic base as acid scavenger can reduce side reactions, as long as no water is generated during neutralization. K_3PO_4 was chosen because it led to the highest yield and posed no reduction risk to the substrate as K_2SO_3 would.

The results of a solvent screen with 2.5 equiv of K_3PO_4 are given in Table 2. Multiple products and low yields were observed in MeCN and DMF (entries 2 and 3), probably due to reactions between **4** and these solvents. More hydrolysis was found in dioxane and toluene (entries 4 and 5), where the coupling rates are much slower. Among the solvents evaluated, THF gave the best result.

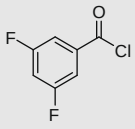
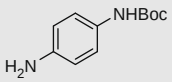
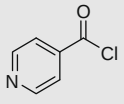
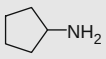
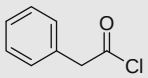
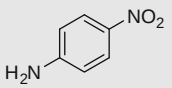
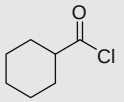
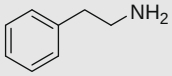
The established condition[8] was next applied to various amide formation reactions and the results were compared with those under literature conditions (Table 3). All the reactions were completed in less than 30 min. When triethylamine was used as base, high yields were obtained provided there were no α-protons in the acyl chloride (entries 1 and 2). Isolated yields dropped significantly when the acyl chloride contained a α-proton (entries 3 and 4). When aqueous NaOH was employed, the degree of hydrolysis of the corresponding acyl chloride depended as expected on the rate difference between amide bond formation and hydrolysis. As given in entry 3, phenylacetyl chloride **4** was hydrolyzed exclusively with sodium hydroxide, when the amine (4-nitroaniline **8c**) had low nucleophilicity. Couplings with K_3PO_4 however, gave excellent yields in all cases, showing no substrate dependency.

The couplings[9] between acyl chlorides and unprotected amino acids were examined next (Table 4) Modest results were obtained when triethylamine was used as base, presumably due to the formation of ketene intermediate under these conditions, which led to numerous side reactions (entries 2–4). When aqueous NaOH was used, the outcome was controlled by the property of the amino acid. Alanine **8e** was observed to self-condense under basic condition.[10] When used in the presence of aqueous NaOH or triethylamine, more than half of the 3-nitrobenzoyl chloride **7e** was hydrolyzed because there was not enough alanine left in the system to react with **7e**. This has also been confirmed by an experiment in which 3 equiv of alanine was used in the presence of aqueous NaOH and the yield was boosted to 88%. When electron-deficient 4-aminobenzoic acid **8f** was reacted with 3-methoxyphenylacetyl chloride **7f** and aqueous NaOH, almost 80% of **7f** was hydrolyzed. The reaction with potassium phosphate is relatively slower, mainly due to the heterogeneous character of the reaction (liquid acyl chloride, solid potassium phosphate, and solid amino

Table 3
Coupling of primary amines with acyl chlorides[a]

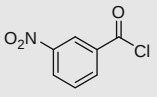
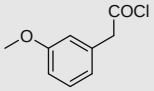
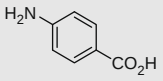
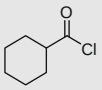
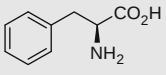
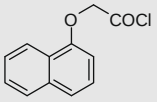
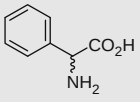


7 **8** **9**

Entry	7	8	Base	Yield (%)
1	 (**7a**)	 (**8a**)	Et_3N	88 (**9a**)
			NaOH	81 (**9a**)
			K_3PO_4	94 (**9a**)
2	 (**7b**)	 (**8b**)	Et_3N	84 (**9b**)
			NaOH	92 (**9b**)
			K_3PO_4	99 (**9b**)
3	 (**4**)	 (**8c**)	Et_3N	30 (**9c**)
			NaOH	5 (**9c**)[b]
			K_3PO_4	95 (**9c**)
4	 (**7d**)	 (**8d**)	Et_3N	42 (**9d**)
			NaOH	84 (**9d**)
			K_3PO_4	96 (**9d**)

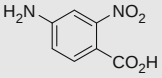
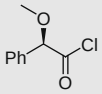
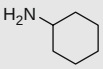
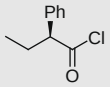
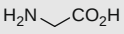
[a] Product yields have not been optimized. The products are purified by flash column chromatography.
[b] Corresponding phenylacetic acid is the only byproduct and accounted for 95% of mass balance.

Table 4
Coupling results with different unprotected amino acids under different conditions[a]

Entry	7	8	Base	Yield (%)
1	 (**7e**)	 (**8e**)	Et_3N	30 (**9e**)
			NaOH	46 (**9e**)
			K_3PO_4	86 (**9e**)
2	 (**7f**)	 (**8f**)	Et_3N	62 (**9f**)
			NaOH	23 (**9f**)
			K_3PO_4	89 (**9f**)
3	 (**7c**)	 (**5**)	Et_3N	42 (**9g**)
			NaOH	93 (**9g**)
			K_3PO_4	90 (**9g**)
4	 (**7h**)	 (**8h**)	Et_3N	42 (**9h**)
			NaOH	92 (**9h**)
			K_3PO_4	88 (**9h**)

[a] Product yields have not been optimized. The products are purified by flash column chromatography.

Table 5
Coupling results with chiral acyl chlorides[a]

Entry	7	8	Base	Yield/ee[b] (%)
1	 (**7i**)	 (**8i**)	Et_3N	80/97 (**9i**)
			NaOH	**28/>99 (9i)**
			K_3PO_4	**98/>99 (9i)**
2	 (**7j**)	 (**8j**)	Et_3N	88/>99 (**9j**)
			NaOH	92/>99 (**9j**)
			K_3PO_4	96/>99 (**9j**)
3[c]	 (**7k**)	 (**8k**)	Et_3N	5/71 (**9k**)
			NaOH	29/97 (**9k**)
			K_3PO_4	82/97 (**9k**)

[a] Product yields have not been optimized. The products are purified by flash column chromatography.
[b] Enantiomeric excesses were determined by chiral HPLC using both enantiomeric isomers as standard.
[c] The enantiomeric excess of **7k** is 97%.

acid potassium salt). Regardless of the reactivity or stability of the substrates, yields were reliably 85–90% (entries 1–4). Clearly coupling of acyl chlorides with unprotected amino acids using K_3PO_4 is much more practical than that using triethylamine or aqueous NaOH. The procedure had been successfully applied in our research program to produce over 500 g desired product.[11]

The final phase of our examination involved couplings between chiral acyl chlorides and a variety of amines (Table 5). When (*R*)-2-phenoxy-propionyl chloride **7i** was reacted with 4-amino-2-nitrobenzoic acid **8i** (entry 1), the low reactivity of **8i** caused more than 70% hydrolysis when NaOH was used as base. When triethylamine was employed, side reactions and slight racemization were observed. Both degradation and racemization were suppressed, however, when potassium phosphate was used as base. The reaction between (*R*)-2-methoxy-2-phenyl-acetyl chloride **7j** and cyclohexylamine **8j** proved robust and resulted in no racemization under all conditions examined (entry 2). When (*S*)-2-phenylbutyryl chloride **7k** was coupled with glycine **8k** (entry 3), as suspected, the polymerization of glycine[12] under basic conditions complicated the reactions with either aqueous NaOH or triethylamine. Hydrolysis under aqueous conditions, and a significant loss in chirality with an organic base were observed. For comparison, the reaction using potassium phosphate furnished 82% of the desired product without detectable racemization.

In summary, a simple, mild, and highly efficient condition for amide formation using acyl chlorides has been developed. The method is scalable and the reaction offers good to excellent yields with a variety of substrates. The developed reaction conditions greatly minimize the possibility for hydrolysis, racemization, and other unwanted side reactions that usually occur during amide formation with acyl chlorides. The methodology is extremely economical, as simple inorganic bases can replace the use of expensive coupling reagents and increase the utility of acyl chlorides in amide synthesis.

Acknowledgments

We thank Dr. Carl Busacca for insightful discussion. We thank Dr. Heewon Lee for her assistance with chiral HPLC method development and monitoring.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.220.

References and notes

1. Stryer, L. In *Biochemistry*, 4th ed.; W.H. Freeman: New York, 1995; p 17. Chapter 2.
2. Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55.
3. Termistoteles, D. *J. Appl.* **1983**, *509*, 442.
4. Montalbetti, C.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.
5. Bouron, E.; Goussard, G.; Marchand, C.; Bonin, M.; Pannecoucke, X.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 7227.
6. Ghosh, S.; Elder, A.; Guo, J.; Mani, U.; Patane, M.; Carson, K.; Ye, Q.; Bennett, R.; Chi, S.; Jenkins, T.; Guan, B. *J. Med. Chem.* **2006**, *49*, 2669.
7. Barton, P.; Laws, A. P.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1994**, *9*, 2021.
8. *General procedure for coupling with amines* (Table 3, **9a**–**9d**). A solution of acyl chloride (2 mmol) in THF (4 mL) was cooled to 0 °C under nitrogen. Potassium phosphate (530 mg, 2.5 mmol) was added in one portion followed by the addition of amine **8** (2 mmol). The mixture was allowed to react for 1 h at rt. The reaction was quenched with water (6 mL) and EtOAc (2 mL). The organic layer was evaporated under vacuum. The crude product was purified either by crystallization or by silica gel column chromatography.
9. *General procedure for coupling with amino acids* (Table 4, **9e**–**9h**). A solution of acyl chloride (2 mmol) in THF (4 mL) was cooled to 0 °C under nitrogen. Potassium phosphate (1.06 g, 5.0 mmol) was added in one portion followed by the addition of amino acid **8** (2 mmol). The mixture was allowed to react for 12 h at rt. The reaction was quenched with water (10 mL) and EtOAc (4 mL). The organic layer was discarded. The pH of aqueous layer was adjusted to 2 by 2 N HCl. The product was extracted with EtOAc (10 mL) and washed with water (6 mL). The organic layer was evaporated under vacuum. The crude product was purified either by crystallization or by silica gel column chromatography.
10. (a) Fischer, E. *Chem. Ber.* **1906**, 3988; (b) Danger, G.; Boiteau, L.; Cottet, H.; Pascal, R. *J. Am. Chem. Soc.* **2006**, *128*, 7412.
11. *Scale-up procedure for coupling with amino acids* (Table 4, **9h**). A solution of 2-(naphthalen-1-yloxy)-acetyl chloride **7 h** (463 g, 2.10 mol) in THF (6 L) was cooled to 0 °C under nitrogen. D,L-Phenylglycine **8h** (302 g, 2.00 mol) was added followed by potassium phosphate (929 g, 4.37 mol). The mixture was allowed to react for 12 h at rt. The reaction was quenched with water (4 L). Most of the THF (5 L) was distilled and MeCN (6 L) was added. The pH was adjusted to 2–3 by 1 N HCl (4.4 L) and the reaction mixture was filtered. The cake was washed with 1:1 MeCN/water (4 L) to afford **9h** as a white solid (576 g, 86% yield).
12. Tsuhako, M.; Ohashi, S.; Nariai, H.; Motooka, I. *Chem. Pharm. Bull.* **1982**, *30*, 3882.